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PATENT SPECIFICATION

NO DRAWINGS

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Inventors: PHILIP ARTHUR KINGSBURY and ROY VIVIAN FOSTER

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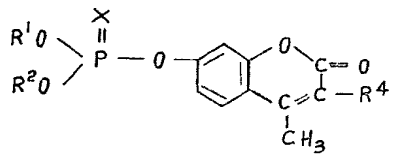
COMPLETE SPECIFICATION

Anthelmintic Compositions containing Phenothiazine

We, COOPER, MCDOUGALL & ROBERTSON LIMITED, a Company incorporated in England, of Berkhamstead, Hertfordshire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to compositions containing phenothiazine and one or more esters, and to the manufacture thereof.

It has been found that a composition containing phenothiazine and a relatively small proportion (as hereinafter defined) of an ester of formula (I) has a greater than additive effect against infestations of the nematodes *Trichostrongylus* spp., in particular *T. colubriformis* and *T. vitrinus*, and *Strongyloides papillosus* in sheep.



(I)

In formula (I):

R^1 and R^2 are the same or different and each is an alkyl group such as a methyl, ethyl or isopropyl group;

X is an oxygen or sulphur atom; and

R^4 is a hydrogen or halogen atom.

The phrase "greater than additive effect" is to be understood as meaning that the effect of the simultaneous administration to an animal of the active components of the said composition at a specified dose level is greater than the sum of the effects of each of the active components at the respective specified dose levels when administered separately to separate animals; and therefore the therapeutic index of the composition is greater than that of each of the active components.

According to the present invention in one aspect, there is provided a composition containing by weight 100 parts of phenothiazine and 0.10 to 10.0 parts of one or more esters of formula (I).

The preferred composition contains by weight 100 parts of phenothiazine and 0.25 to 3.0 parts of one or more esters of formula (I). The preferred esters of formula (I) are those in which R^1 and R^2 are both ethyl groups, especially 3 - chloro - 4 - methyl - 7 oxycoumarin - *O,O* - diethyl-phosphoric and -thiophosphoric, and 4 - methyl - 7 - oxycoumarin - *O,O* - diethylphosphoric acid esters.

The effective dose range of the composition to be administered to the host depends on a number of variable factors, for example the particular ester of formula (I), the parasite to be controlled, the maturity and health of the host, and the mode and frequency of administration of the composition. The amount of phenothiazine in a dose of the composition is preferably not greater than 800 mg./kg. for administration to sheep and 400 mg./kg. to cattle, and not less than 50 mg./kg. for administration to sheep and cattle. The amount of an ester of formula (I) in a dose of the composition is preferably not greater than 5.0 mg./kg. for administration to sheep and 10.0 mg./kg. to cattle, and not less than 0.5 mg./kg. for administration to sheep and to cattle. The preferred dose of the composition contains 100 to 400 mg./kg. of phenothiazine and 1.0 to 3.0 mg./kg. of an ester of formula (I).

The above mentioned worms, *T. colubriformis*, *T. vitrinus* and *S. papillosus* are members of the toxonomic phylum *Nematoda*, which comprises worms parasitic in mammals and other animals. *Trichostrongylus* spp. also known as bankrupt worms are found in the

small intestine of ruminants and heavy numbers have proved pathogenic in lambs causing the so-called 'black-scour'. Heavy infections of *Strongyloides* spp. are found in the small intestine of young lambs and calves where they may cause severe diarrhoea.

Compositions of the present invention are effective in combating infestations of the above mentioned worms, as well as other nematodes such as *Ostertagia* spp., *Nematodirus* spp. This invention therefore provides a method for the treatment of an infestation of nematodes in a domestic animal, particularly a sheep, comprising the administration of a composition as hereinbefore defined.

The composition is preferably administered orally in any acceptable preparation. Fine powders or granules may contain diluents and dispersing and surface active agents, and may be presented in a draft or drench in water or in a syrup; in capsules or cachets in the dry state or in a non-aqueous suspension, when a suspending agent may be included; in tablets, when binders and lubricants may be included; in a suspension in water or a syrup or an oil, or in a water-oil emulsion, when flavouring, preserving, suspending, thickening and emulsifying agents may be included; or in the food of the host of the nematode i.e. in an animal feeding stuff. The granules or the tablets may be coated. The preferred preparations for administration are fine dispersible powders, tablets and emulsions.

According to the present invention in another aspect, there are provided veterinary preparations for oral administration containing the composition and an acceptable carrier therefor.

The composition or the preparations containing the composition and an acceptable carrier therefor may be manufactured by any method comprising respectively the mixing together of the active components of the composition, and the mixing together of the active components of the composition and an acceptable carrier therefore.

According to the present invention in yet further aspects, there are provided the methods of manufacturing the composition, and the preparations containing the composition and an acceptable carrier therefor.

The invention will now be described with reference to the following examples in which the amounts of the constituents are indicated in parts by weight.

EXAMPLE 1

Phenothiazine	96.5%
3-Chloro-4-methyl-7-oxycoumarin-*O,O*-diethyl phosphoric acid ester	0.5%
A wetting and dispersing agent, such as a sodium salt of an alkylarylsulphonic acid	3.0%

A fine dispersible powder was prepared by grinding the phenothiazine, mixing some of the phenothiazine with the 3 - chloro - 4-methyl - 7 - oxycoumarin - *O,O* - diethylphosphoric acid ester and the wetting, dispersing agent, adding the rest of the phenothiazine to the mixture, and intimately mixing the resultant mixture.

EXAMPLE 2

Phenothiazine	92.1%
3-Chloro-4-methyl-7-oxycoumarin-*O,O*-diethylphosphoric acid ester	0.5%
A binding agent such as starch	4.6%
A dispersing agent, such as sodium bicarbonate	1.9%
A lubricating agent, such as talc	0.9%

Tablets of the above composition and weighing 5.0 g. were prepared by intimately mixing the ingredients together, granulating the mixture, and compressing the granules.

EXAMPLE 3

3 - Chloro - 4 - methyl - 7 - oxycoumarin-*O,O* - diethylphosphoric acid ester (1 part) was mixed with a diatomaceous earth known as "Celite 209" (Registered Trade Mark) (4 parts) in a ball mill. The mixture (3.33 parts) was mixed with a dispersible powder of phenothiazine (96.67 parts; 92% technical phenothiazine and 8% of a wetting and dispersing agent containing a sodium salt of an alkylarylsulphonic acid). The resulting powder dispersed in water and was suitable for administering a dose of 200 mg./kg. technical phenothiazine together with 1.5 mg./kg. of the ester.

EXAMPLE 4

3 - Chloro - 4 - methyl - 7 -oxycoumarin-*O,O* - diethylthiophosphoric acid ester (1 part) was mixed in a mill with a dispersible powder of phenothiazine (5 parts; 92% technical phenothiazine and 8% of a wetting and dispersing agent containing a sodium salt of an alkylarylsulphonic acid). More of the dispersible powder of phenothiazine (104 parts) was added to the mixture. The resulting powder dispersed in water and was suitable for administering a dose of 200 mg./kg. technical phenothiazine together with 2 mg./kg. of the ester.

EXAMPLE 5

Preparations similar to those described in Examples 1, 2 and 3 were manufactured using 3 - chloro - 4 - methyl - 7 - oxycoumarin-*O,O* - diethylthiophosphoric or 4 - methyl-7 - oxycoumarin - *O,O* - diethylphosphoric acid ester instead of the 3 - chloro - 4-methyl - 7 - oxycoumarin - *O,O* - diethylphosphoric acid ester.

EXAMPLE 6

Compositions were made by mixing the following components, the amount of each component being specified respectively as the amount in mg./kg. administered to the host.

a) Phenothiazine and 3 - chloro - 4-methyl - 7 - oxycoumarin - *O,O* - diethylthiophosphoric acid ester:

(i)	1000 and 2.5
(ii)	500 and 2.5
(iii)	400 and 2.5
(iv)	300 and 2.5
(v)	200 and 2.5
(vi)	100 and 2.5
(vii)	200 and 2.0
(viii)	500 and 1.0
(ix)	500 and 0.5

b) Phenothiazine and 3 - chloro - 4-methyl - 7 - oxycoumarin - *O,O* - diethylphosphoric acid ester:

(i)	500 and 2.0
(ii)	400 and 2.0
(iii)	200 and 2.0
(iv)	100 and 2.0
(v)	50 and 2.0
(vi)	200 and 1.5
(vii)	500 and 1.0
(viii)	200 and 1.0
(ix)	500 and 0.5
(x)	100 and 0.5

c) Phenothiazine and 4 - methyl - 7-oxycoumarin - *O,O* - diethylphosphoric acid ester:

(i)	500 and 3.0
(ii)	200 and 2.0
(iii)	100 and 2.0
(iv)	200 and 1.0

d) Phenothiazine and 3 - bromo - 4-methyl - 7 - oxycoumarin - *O,O* - diethylthiophosphoric acid ester:

500 and 5.0

e) Phenothiazine and 3 - chloro - 4-methyl - 7 - oxycoumarin - *O,O* - dimethylthiophosphoric acid ester:

500 and 20.0

f) Phenothiazine and 3 - chloro - 4-methyl 7 - oxycoumarin - *O,O* - di - isopropylthiophosphoric acid ester.

500 and 25.0

g) Phenothiazine and 4 - methyl - 7-oxycoumarin - *O,O* - diethylthiophosphoric-acid ester:

500 and 3.0

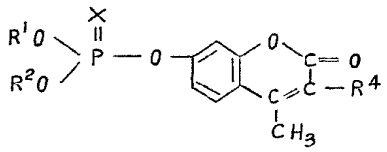
EXAMPLE 7

a) 4 - Methyl - 7 - oxycoumarin - *O,O*-diethylphosphoric acid ester was prepared by reacting 4 - methyl - 7 - hydroxycoumarin with *O,O* - diethylphosphite and had a refractive index of 1.5458.

b) 3 - Chloro - 4 - methyl - 7 - oxycoumarin - *O,O* - di - isopropylthiophosphoric acid ester was prepared by reacting 3 - chloro-4 - methyl - 7 - hydroxycoumarin and di-isopropyl thiophosphoryl chloride and had a melting point of 120°C.

WHAT WE CLAIM IS:—

1. A composition containing by weight 100 parts of phenothiazine and 0.10 to 10.0 parts of one or more esters of the formula:



wherein R^1 and R^2 are the same or different and each is an alkyl group, X is an oxygen or sulphur atom, and R^4 is a hydrogen or halogen group.

2. A composition as claimed in claim 1 containing by weight 100 parts of phenothiazine and 0.25 to 3.0 parts of one or more esters of the defined formula.

3. A composition as claimed in claim 1 or 2 wherein the ester has both R^1 and R^2 as ethyl groups.

4. A composition as claimed in claim 1 or 2 wherein the ester is 3 - chloro - 4 - methyl-7 - oxycoumarin - *O,O* - diethylphosphoric acid ester.

5. A composition as claimed in claim 1 or 2 wherein the ester is 3 - chloro - 4-methyl - 7 - oxycoumarin - *O,O* - diethylthiophosphoric acid ester.

6. A composition as claimed in claim 1 or 2 wherein the ester is 4 - methyl - 7 - oxycoumarin - *O,O* - diethylphosphoric acid ester.

7. A veterinary preparation for oral-administration containing a composition as claimed in any of claims 1 to 6 and an acceptable carrier therefor.

8. An animal feeding stuff containing a

composition as claimed in any of claims 1 to 6.

9. A method of manufacturing a composition as claimed in any of claims 1 to 6 which comprises the mixing together of the active components of the said composition.

10. A method of manufacturing a preparation as claimed in claim 7 which comprises the mixing together of the active components of the composition and an acceptable carrier therefor.

11. A method of manufacturing a composition substantially as hereinbefore described with reference to any of the foregoing examples 1 to 6 or any obvious equivalent.

12. A composition according to claim 1 substantially as herein described or ascertained or any obvious equivalent.

13. A method for the treatment of an infestation of nematodes in a domestic animal, particularly a sheep, comprising the administration of a composition defined in any one of claims 1 to 6.

R. F. HASLAM,
Agent for the Applicants.

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